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Insights and Perspectives on Sensory-Motor Integration and Rehabilitation

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Abstract

The present review focuses on the flow and interaction of somatosensory-motor signals in the central and peripheral nervous system. Specifically, where incoming sensory signals from the periphery are processed and interpreted to initiate behaviors, and how ongoing behaviors produce sensory consequences encoded and used to fine-tune subsequent actions. We describe the structure–function relations of this loop, how these relations can be modeled and aspects of somatosensory-motor rehabilitation. The work reviewed here shows that it is imperative to understand the fundamental mechanisms of the somatosensory-motor system to restore accurate motor abilities and appropriate somatosensory feedback. Knowledge of the salient neural mechanisms of sensory-motor integration has begun to generate innovative approaches to improve rehabilitation training following neurological impairments such as stroke. The present work supports the integration of basic science principles of sensory-motor integration into rehabilitation procedures to create new solutions for sensory-motor disorders.

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1. Introduction

Presently, we aim to unravel the nature and mechanisms responsible for the ability to organize sensory perceptions and motor routines, in order to open a window onto the organization of the somatosensory-motor loop. We will focus on somatosensory input and how this is processed and integrated centrally, to determine motor behavior. The fine balance between sensory input and motor output is essential for efficient interactions within the environment, and also includes the integration of incoming multisensory signals (e.g., vision, hearing, touch). Somatosensory feedback is pertinent for the fine tuning of dexterous movements. If this is impaired due to trauma or injury, due to, e.g., stroke or spinal cord injury, the incoming somatosensory signals are degraded and the effects can be very detrimental. In these cases, the absence of precise somatosensory feedback can render patients unable to perform movements despite the fact that basic motor function is relatively preserved (Ionta *et al.*, 2016). In recent years, there have been important updates on the basic mechanisms, anatomo-functional neural basis, and rehabilitation procedures of such sensory-motor integration. Furthering the understanding of healthy and pathological somatosensory-motor integration mechanisms is essential and supports a theoretical model as general reference framework, with direct clinical outcomes.

In the next section we will provide a broad overview of state-of-the-art functional neuroimaging evidence on the interaction between somatosensory afferent information and efferent movement control, with a particular focus on touch. The third section will summarize the relationship between structural neuroimaging data and clinical phenotypes of sensory-motor disorders. In the fourth section we will discuss behavioral data within the framework of theoretical generalizations and modeling of the sensory-motor loop. The last section will discuss mechatronic tactile stimulation platforms developed in order to enable human touch studies with psychophysical and electrophysiological methods.

2. Functional Bases of Somatosensory-Motor Processing

The physiological investigation of the somatosensory system has its roots in pioneering studies of experimentalists such as Adrian, who investigated the afferent impulses from peripheral nerves (Adrian, 1926) and Penfield, who used electrical stimulation to map the sensorimotor cortex (Penfield and Boldrey, 1937). Somatosensory-motor interactions are engrained in the fast conducting information that is sent to (afference) and from (efference) the central nervous system (Fourkas *et al.*, 2006). The inherent accuracy and precision in this system allows us to engage in complex tasks, such as picking up a slippery object. It also provides a wealth of information for exploratory and manipulative tactile interactions with objects, allowing us to distinguish between multitudes of surfaces. Thus, for accurate motor control and exploration of the world, fast sensorimotor integration is essential. This is achieved through the comparison of motor behavior and its somatosensory consequences, with the inclusion of other factors, such as multisensory information (especially visual and auditory signals) and cognitive mechanisms, including experience, memory and learning.

Functional human brain imaging has provided us with a wealth of information about sensory and motor processes, and how these interact at a systems level. Nevertheless, we have much to learn about the normal functioning of these processes. One of the most immediate consequences of interacting physically with the environment is tactile perception. Concerning touch input, most studies have focused on afferent input to the primary somatosensory cortex (S1) to investigate how tactile information is processed; however, there are many other areas that contribute to decoding touch. The first stage in this process is the mechanoreception of interactions between the skin and external objects. Many different types of mechanoreceptive (touch) afferent contribute to somatosensation and the information transmitted depends on where the touch is received. The skin can be categorized by whether it is glabrous (non-hairy, e.g., the palms of the hands, soles of the feet) or hairy (the majority of the skin on the body). Different mechanoreceptive afferents are found at varying densities in the skin, which contribute to somatosensation by encoding various aspects of touch. The glabrous skin contains only fast conducting, myelinated mechanoreceptive afferents (see Fig. 1). These are densely packed in the glabrous skin and capable of encoding detailed aspects of touch, for example, pressure, force, vibration, edges, features and textures (Johnson, 2001). Additional types of fast conducting, myelinated afferents are found in hairy skin as well as slowly conducting, unmyelinated C-tactile (CT) afferents (Vallbo *et al.*, 1993, 1995) (Fig. 1). Myelinated afferents are more sparsely found in the hairy skin, which contributes to its decreased tactile discrimination capabilities, as compared to the glabrous skin (Ackerley *et al.*, 2014a; Weinstein, 1968). Thus the type of touch and where it is applied to the skin may result in different behaviors, depending on the afferents activated.

Once a tactile stimulus has been registered by these afferents, the information is sent to the spinal cord, before being relayed to S1, where tactile information is processed and integrated cortically (Mountcastle, 1957) (Fig. 1). This is the classical pathway for touch to reach the brain; however there are

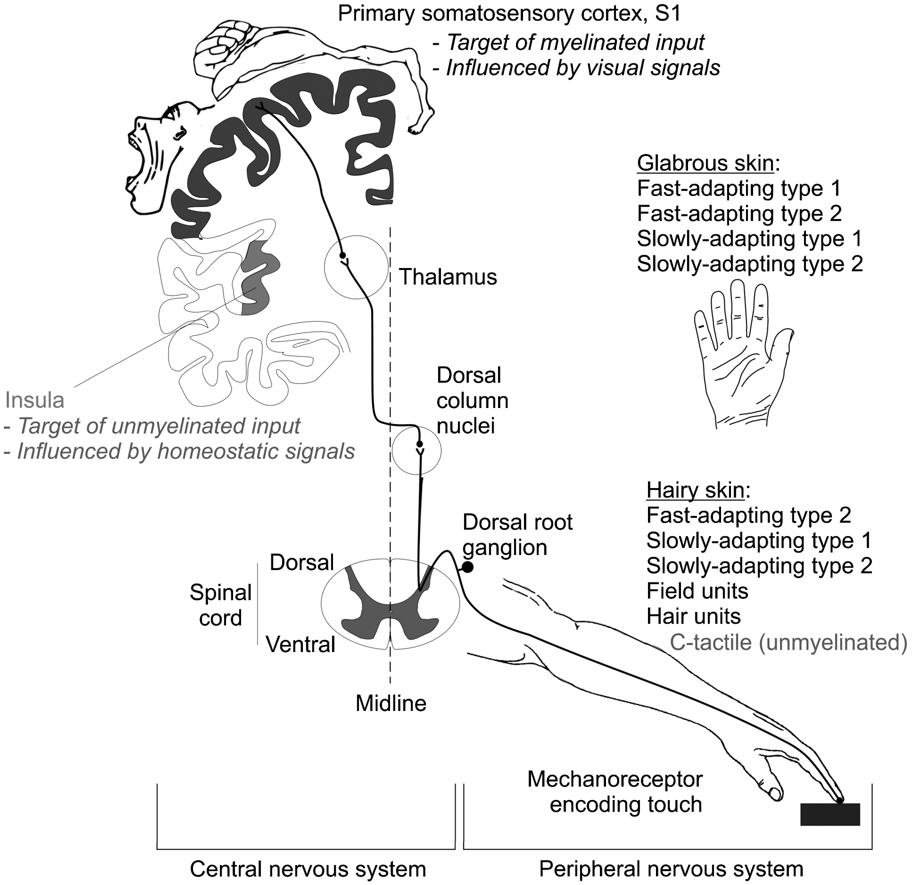

Figure 1. Overview of touch pathways from the periphery to brain. Once a tactile stimulus has been registered by mechanoreceptors in the skin, the information is sent to the primary somatosensory cortex (S1) or the insula, which are both somatosensory regions with different multisensory influences.

other ways that tactile information enters the brain (e.g., from CT afferents that project to the insula) and the processing of touch occurs over many different levels (Ackerley and Kavounoudias, 2015). The central target of touch information will in turn determine how the signals are processed, where the insula target is likely to be combined with much more emotional related information (e.g., with homeostatic mechanisms) and S1 with discriminative information (e.g., with vision) (Ackerley and Kavounoudias, 2015). The majority of mechanoreceptive research has focused on the touch from glabrous skin of the hands, due to its essential function in everyday life, which is exemplified in the amount of cortex dedicated to it, as seen by the proportionally greater representations in both the sensory and motor homunculi (Fig. 1). With advances in functional imaging technology, especially ultrahigh field (e.g., 7 Tesla, 7T) functional magnetic resonance imaging (fMRI), it is now possible to explore S1 in exquisite detail. Studies have shown precise intra- and interdigital representations in the subsections of S1 (i.e., Brodmann areas 3b, 1 and 2) (Martuzzi *et al.*, 2014; Sanchez-Panchuelo *et al.*, 2010, 2012; Stringer *et al.*, 2011).

S1 is central to somatosensory-motor processing, as it receives the bulk of myelinated tactile information from the periphery, which is sent from the thalamus in a somatotopic fashion (homunculus), as found through the historic electrical mapping experiments of Penfield (Penfield and Boldrey, 1937; Rasmussen and Penfield, 1947). These pioneering experiments demonstrated that the human primary sensory and motor (M1) cortices show a distinct body map, where body parts with higher discriminative abilities are represented by larger cortical space and that the sensory and motor cortices are inexplicably linked in function. The precentral (motor) and postcentral (sensory) gyri both have these body map representations and they function together to aid in somatosensory integration. This was shown through electrical cortical stimulation, where S1 can produce movements and M1, sensation; hence these areas are not exclusively sensory and motor, respectively (Penfield and Boldrey, 1937). This is especially evident for the stimulation of the hand cortical areas, likely due to the large receptive fields dedicated to them and their importance in sensory-motor control. More recent studies have found further evidence for the close relationship between somatosensory and motor interactions, such as direct S1–M1 projections (Huerta and Pons, 1990), that S1 can drive exploratory protraction of the whiskers in mice (Matyas *et al.*, 2010) and that the excitability of M1 is continuously modulated by somatosensory afference, especially during precise, fine motor control in humans (Tamburin *et al.*, 2001).

The interplay between somatosensory and motor integration is highlighted in differences in the processing of active (self generated) and passive (other) touch. The similarity between active and passive touch is that near identical tactile afference may be generated provided that tactile stimulation platforms are properly tailored to the experimental framework (as discussed in Section 5); however, during active touch, motor commands (efference copy) are issued that can shape the meaning of the tactile feedback, as well as there being predictive mechanisms, such as through internal models (Wolpert *et al.*, 1995). M1 plays a critical role in the execution of motor behavior and it has been postulated that tactile signals integrated into M1 may contribute to perception in active touch (Ferezou *et al.*, 2007), for example, where the activity in M1 is modified by both the weight and texture of a grasped object (Picard and Smith, 1992). S1 is also modulated by active and passive touch (Ionta *et al.*, 2014). A network of cortical areas, including the contralateral S1, bilateral secondary somatosensory cortex (S2) and posterior parietal cortex (PPC), is activated during all types of touch (Ackerley *et al.*, 2012; Disbrow *et al.*, 2000; Francis *et al.*, 2000; Ruben *et al.*, 2001). The contralateral M1 can also be activated during passive touch to the glabrous skin of the hands (Ackerley *et al.*, 2012; Francis *et al.*, 2000).

Active touch typically produces sensations that are less intense, as compared to passive touch (Ackerley *et al.*, 2014b); however, this is not always the case, especially when the person seeks tactile information such as during the exploration of a surface for specific features. The classical idea of why you cannot tickle yourself (active self touch, compared to being tickled by another) captures the dynamic relationship between the processing of afference from self generated and other generated tactile signals (Blakemore *et al.*, 1998, 2000; Weiskrantz *et al.*, 1971). An efference copy signal from the motor intention cancels or countermands the incoming sensory consequence. Using fMRI, increased activity was found in S1 when the tickle was externally produced, thus there was a decreased signal during self tickle (Blakemore *et al.*, 1998). The prediction of the sensory consequences of the self tickle meant that the incoming afference produced from self touch was gated out, thus less activity was seen in S1. On the other hand, increases in the signal in S1 during active touch, as compared to passive (other 'generated') touch, have been found in other tactile interactions, where attention is focused on the action and incoming afference (Ackerley *et al.*, 2012; Simões-Franklin *et al.*, 2011). Hence, it seems that there is a complex interaction between somatosensory and motor signals, with other cognitive factors such as attention and intention, which shape the way information is processed in S1.

Other cortical areas play key roles in processing and integrating somatosensory and motor information. S2 contributes to discriminative somatosensory processing, but does not contain the precise somatotopic body representations found in S1, rather the cortical receptive fields are large and overlapping for body areas, as found in monkey work (Fitzgerald *et al.*, 2006; Sinclair and Burton, 1993; Thakur *et al.*, 2006). Neurons in S2 have been found to code for more cognitive aspects of touch, including the stages of motor hand grasping, representations of past and present sensory information, modulations with attention, comparisons between stimuli, correlations with behavioral decisions, and discriminative learning (Hsiao *et al.*, 2002; Ishida *et al.*, 2013; Murray and Mishkin, 1984; Romo *et al.*, 2002a, b). The cerebellum also has a major role in the integration of multisensory and motor signals, where there are dense projections from all over the cortex, including from somatosensory, motor, visual and emotional areas, to the cerebellum (Brodal, 1978; Leergaard and Bjaalie, 2007). Although it is particularly involved in integrating and fine-tuning somatosensory and motor information, it has the capacity for diverse information processing (Cerminara *et al.*, 2015), where an internal model is constructed about the sensory-motor action (Wolpert *et al.*, 1995).

The PPC and premotor cortex (PMC) are activated during haptic sensing, object recognition and sensorimotor transformations during visually guided motor activities, often providing a prehension signal to aid in processing sensory afference (Colby and Duhamel, 1996; Gardner *et al.*, 2007), akin to the integrative role of the cerebellum. This suggests that these areas are key in the predictive and planning components of active touch, whereas S1 and M1 deal with the more immediate components of performance. The PMC in particular has been found to subserve motor and cognitive functions such as coordinating motor intentions and with the understanding of actions (Bonini *et al.*, 2011; Rizzolatti *et al.*, 2002). These two cortical areas have clear multimodal properties including motor, somatosensory and visual functions and contribute to transforming somatosensory information into motor behavior (Candidi *et al.*, 2008). The influence of visual signals can also be found in somatosensory-motor processing. For example, coincident visual and tactile stimuli on human hands activates both the PMC and intraparietal sulcus for visuotactile integration (Gentile *et al.*, 2011). Vision can modulate responses in S1, especially when the viewed stimulus implies tactile interactions or touch is observed (Meyer *et al.*, 2011; Pihko *et al.*, 2010). For instance, recent studies demonstrated the influence of vision over somatosensory processing in human–object and human–human interactions based on visuotactile integration (Ebisch *et al.*, 2011; Ionta *et al.*, 2013; Rossetti *et al.*, 2012; Schaefer *et al.*, 2009). These findings imply a more cognitive or emotional aspect to the modulation of somatosensory areas by visual signals.

Visuotactile interactions are pertinent in our everyday lives and the combination of incoming tactile and visual signals together with cognitive mechanisms such as memory, learning, attention, expectation and prediction, shape our behavior. The integration of human touch information is more dependent upon these higher level processes; however, it is postulated that positive affective tactile information is signaled directly by unmyelinated CT afferents that are only found in hairy skin and respond preferentially to gentle stroking touch (Ackerley *et al.*, 2014c; Löken *et al.*, 2009). These afferents encode pleasant social interactions at a basic level and send information to the insular cortex, known for its multisensory role in emotion and bodily regulation, as compared to the discriminative information sent to S1 (McGlone *et al.*, 2014; Olausson *et al.*, 2002). The multisensory experience of human touch, and its behavioral consequence, is therefore not just limited to tactile discrimination, but also includes visual, affective and emotional variables, such as pleasantness and arousal (Ackerley *et al.*, 2014b), which affect the seeking or avoidance of somatosensory-motor interactions. For example, pleasant encounters will be interpreted as positive and be reinforced, whereas unpleasant situations will be dissuaded, aiding in the production of appropriate behavior.

3. Structural Approaches to Study the Pathology of the Somatosensory-Motor Loop

New advances in neuroimaging and neurostimulation approaches have begun to unravel the salient neural substrates underlying persisting motor dysfunction in a number of neurologic conditions (Borich *et al.*, 2013b). A renewed interest has been placed on understanding and mapping the anatomical circuits that support neural function in the human brain. In this vein, recent work has evaluated the structural properties underlying multisensory mechanisms of somatosensory interactions (Brang *et al.*, 2013; Van den Brink *et al.*, 2014) demonstrating the importance of characterizing the anatomical substrates underlying multisensory function. For instance, a recent emphasis has been placed on studying the human brain connectome (Sporns *et al.*, 2004) in an attempt to identify the underlying neuroanatomical connections in the brain that are necessary to understand the complex organization of local and distributed information processing. Currently, white matter imaging techniques (diffusion imaging, relaxometry, etc.) are the gold standard for noninvasively characterizing structural properties of brain networks. These new approaches can probe the brain architecture, providing insights on the effective integration of information across different sensory modalities to better shape motor outputs. From a rehabilitation and motor learning perspective, it has been shown that differences in brain structure after injury or in the context of neurologic disorders are associated with alterations in behavior (Avanzino *et al.*, 2015). When combined with noninvasive brain stimulation (NIBS) approaches, structural imaging also offers exciting novel avenues to study brain structure–function relationships contributing to normal and abnormal sensory-motor function. The most common cause of adult disability is stroke and disability is largely due to disruption of the somatosensory motor loop resulting in motor dysfunction and decreased quality of life. Stroke provides a testable model to characterize the anatomical substrates of both normal and abnormal sensory-motor function and the potential for these substrates to be modified by experience. Additionally, in the rehabilitation literature, there has been a long term focus on stroke thus generating a large amount of knowledge regarding the underlying structural and functional correlates of disability and recovery. While there are clear differences in pathophysiology between stroke and other clinical populations, stroke provides a good model to study restorative and compensatory brain reorganization in response to relatively localized damage. Additionally, a large number of studies have demonstrated that the principles of experience-dependent neuroplastic change (which underlies motor skill learning in healthy individuals) apply to the relearning of previously acquired motor skills or the acquisition of new motor skills in patients after stroke. Thus, focusing on stroke provides a reasonably well characterized model to study adaptive brain reorganization that supports restitution of function that is translatable into other clinical populations.

Using structural magnetic resonance imaging (sMRI) and diffusion weighted imaging (DWI), differences in gray and white matter structure have been demonstrated after stroke. These differences have the capacity to predict levels of sensory-motor dysfunction and response to rehabilitation in patients with stroke. In the context of neurologic disorders (e.g., Parkinson's disease) or after neurologic insult (e.g., stroke), the capacity for performing skilled movements is diminished. In the majority of cases, individuals do not regain previous levels of skill leading to persistent motor dysfunction and decreased quality of life (Edwards *et al.*, 2010; Go *et al.*, 2013). However, the capacity for learning new motor skills or relearning previous skills is rarely abolished. In both the context of heath and disease, motor skill learning is represented by structural and functional neuroplastic change in the brain. Neuroplastic change is constantly occurring and is influenced by a number of factors including characteristics of training (for review: Kleim and Jones, 2008) and processes associated with memory formation (Brashers-Krug *et al.*, 1996; Ionta *et al.*, 2010; Tononi and Cirelli, 2014). Brain imaging can provide a window into structural reorganization following neurologic insult but also into the mechanisms of adaptive plasticity associated with motor skill learning during rehabilitation. Using stroke as a model, the following sections will briefly summarize the current understanding of the influence of brain structure on long term prognosis, current motor performance and residual capacity for motor skill learning. Additionally, evidence for experience-dependent white matter plasticity will be discussed.

The human central nervous system consists of two fundamental types of tissue: gray matter and white matter. Most of the synapses and neurons in the brain are located in gray matter while the axons of neurons and supporting glial cells are primarily found in the white matter. The axons and glial cells are densely packed in white matter tracts that are responsible for information transmission within regions of the brain and between these regions and the rest of the body. One critical feature of white matter is myelin, an extension of glial cell membranes that wraps around axonal fibers to improve conduction velocity and reduce the energy requirements of axons (Van der Knaap and Valk, 2005). Due to the integral role of white matter and its structural organization, injuries in even small volumes of this tissue can have profoundly negative effects on multisensory integration underlying normal behavior.

A broad spectrum of neurologic disorders are associated with white matter pathology; specific examples include multiple sclerosis (MS), stroke, vascular dementia, schizophrenia and traumatic brain injury. In rodent models of both acute (Tanaka *et al.*, 2003) and chronic (Chida *et al.*, 2011) ischemic stroke, white matter degeneration is present. After stroke these changes lead to cognitive learning impairment and their reversal by remyelination is positively associated with cognitive recovery (Chida *et al.*, 2011). In conjunction, recent work suggests that white matter may be an important therapeutic target to reduce the burden of disease associated with certain neurologic disorders (for review: Dobkin, 2007; Stys and Lipton, 2008).

Unique and detailed information about white matter anatomy and brain recovery following stroke can be generated using diffusion weighted imaging (DWI). DWI capitalizes on the diffusive properties of water to determine microstructural integrity of white matter. Fractional anisotropy (FA) is a quantitative, unitless measure of diffusion behavior of water in the brain. It is influenced by microstructural properties of white matter and is the most commonly reported measure of white matter integrity after stroke (Jang, 2010). After stroke, white matter tract integrity can be affected both locally and distally to the primary lesion location (Werring *et al.*, 2000). Abnormal white matter tissue microstructural properties in ipsi- or contralesional descending motor output pathways have been associated with greater levels of physical impairment and motor dysfunction (Borich *et al.*, 2012; Qiu *et al.*, 2011; Stinear *et al.*, 2007), reduced motor learning (Borich *et al.*, 2013a; Stinear *et al.*, 2007), and hand sensory-motor dysfunction (Borich *et al.*, 2012; Borstad *et al.*, 2012; Schaechter *et al.*, 2009). Mean FA values in descending motor output pathways measured acutely after stroke have also been used as part of an algorithm used to predict potential for functional recovery (Stinear *et al.*, 2012).

There is substantial evidence demonstrating positive neuroplastic change after stroke (Boyd and Winstein, 2003; Taub *et al.*, 1993). It has been clearly shown that capacity for neuroplastic change is preserved, even in individuals with chronic stroke (as demonstrated by fMRI and improvements in motor function — Boyd and Winstein, 2003, 2004a, b, 2006; Boyd *et al.*, 2009; Pohl and Winstein, 1999; Velicki *et al.*, 2000; Vidoni and Boyd, 2009; Winstein *et al.*, 1999) (Boyd *et al.*, 2007; Meehan *et al.*, 2011). Although increasing the amount of skilled use of the paretic side induces neuroplastic change in gray matter (Calautti and Baron, 2003; Calautti *et al.*, 2001a, b, 2004; Sawaki, *et al.*, 2008), the dose of movement required is exceedingly high (Lang *et al.*, 2009). Currently, definitive numbers of repetitions needed for optimal learning (Kleim and Jones, 2008) to stimulate neuroplastic change in gray (Luke *et al.*, 2004) or white matter (Scholz *et al.*, 2009) are unknown. What is known is that low doses of task-specific movement practice occur during stroke rehabilitation (Lang *et al.*, 2007, 2009) that are likely suboptimal for inducing lasting structural and functional neuroplastic change to improve sensory-motor network activity underlying behavior. Thus, alternative approaches have been pursued to augment experience-dependent neuroplasticity after stroke.

Following stroke, NIBS may be used to re-establish the altered balance of cortical excitability between the hemispheres (Murase *et al.*, 2004; Shimizu *et al.*, 2004) and/or pre-excite a cortical region that will be engaged in subsequent behavioral practice (Boyd and Linsdell, 2009). Yet, on average, the reported effects of NIBS in individuals with stroke are small (Bell *et al.*, 2008) and varied (Brodie *et al.*, 2014; Carey *et al.*, 2014). Since the first clinical trial of repetitive transcranial magnetic stimulation (rTMS), a common form of NIBS in 2001, a substantial number of investigations have been conducted to evaluate the therapeutic potential of rTMS to modulate cortical activity and improve function after stroke (Lefaucheur *et al.*, 2014). However, due to a number of factors including small sample sizes, heterogeneity of participant characteristics, undefined optimal stimulation parameters and lack of synergistic skill training applications, the positive effects of rTMS on sensory-motor function in stroke have been modest (Hao *et al.*, 2013; Le *et al.*, 2014; Lefaucheur *et al.*, 2014).

Combining structural imaging approaches with NIBS offers opportunities to probe the structure–function relationships contributing to abnormal sensory-motor function and response to NIBS-based interventions. For example, it was shown recently that response to an intervention pairing rTMS over the ipsilesional S1 prior to motor skill training using the paretic arm was predicted by the volume of white matter within ipsilesional S1 as measured by sMRI prior to beginning the intervention (Brodie *et al.*, 2014). This example highlights potential applications of structural imaging approaches to identify potential biomarkers of response to NIBS paradigms to better tailor novel therapeutic interventions to the characteristics of a given individual. Longitudinal imaging assessments of brain structure can capture aspects of anatomical reorganization during stroke recovery but can also be used to monitor neuroplastic change associated with rehabilitation to determine if sufficient experience-dependent plasticity in brain regions involved in multisensory integration is being driven by a given intervention.

For stroke rehabilitation approaches to be maximally effective on a patient-by-patient basis, it is critical to address all sensory systems involved in each functional task of interest. Although incorporating multiple sensory systems during rehabilitation is commonly understood in contemporary treatment approaches, limited research has directly focused on multisensory approaches in a stroke rehabilitation context. Recently a review of multisensory stimulation was published showing positive benefits of concomitantly stimulating multiple sensory areas to improve sensory function after stroke (Tinga *et al.*, 2016). However, a quantitative quality assessment suggested that definitive conclusions could not be reached due to methodological issues of the studies included in the review. Additionally, the multisensory stimulation interventions were focused on sensory function rather than the way a given intervention directly impacts the restoration of motor function. Recently, a pilot study demonstrated the feasibility of a virtual reality-based approach utilizing multisensory feedback during movement to improve motor function (Kato *et al.*, 2015). Although encouraging, the pilot nature of this investigation precludes definitive conclusions regarding the benefits of multisensory approaches in stroke rehabilitation. Although historically not a specific focus of rehabilitation research, it is commonly understood that a multisensory approach is beneficial to stroke rehabilitation but future research to evaluate the degree of benefit of these approaches compared to unisensory approaches would further substantiate current clinical practice.

In the context of motor learning, there are clear advantages of taking a multisensory approach to improve recovery after stroke. During stroke rehabilitation, the recovery of function requires the same memory formation processes underlying motor learning in healthy individuals. Under typical conditions, these motor skill memories are formed using multisensory information from the external and internal environments. For example, recovery of functional paretic arm reach to grasp activities requires processing of multisensory information from the somatosensory system, proprioceptive system and visual system. The advantage of taking a multisensory approach to understand stroke and stroke recovery is that this approach accounts for the role of each sensory system in performing and (re) learning functional movements. Without accounting for one or all of the sensory systems involved in a skilled task during stroke rehabilitation will result in a suboptimal approach to motor skill learning underlying the recovery of function.

4. Modeling Sensory-Motor Integration

Conceiving theoretical models to explain the causal link between dysfunctional brain networks and clinical phenotypes is a major challenge in cognitive neuroscience. In the current models of sensory-motor integration the reciprocal role of somatosensory and motor mechanisms is still unclear. Here we will enclose the reviewed evidence on typical and pathological sensory-motor organization in a general theoretical model of modes and operations of sensory-motor processing.

Classic models of sensory-motor integration postulate that the process as a whole can be broken down into different subaspects (nodes) and that the activity of specific spatiotemporally specialized neural substrates can be attributed to each individual aspect, or node (Sanger and Merzenich, 2000; Shadmehr and Krakauer, 2008; Wolpert *et al.*, 1995). Recent theorizations of sensory-motor integration propose that the first activated nodes encode the movement preparation phase, preloading the sequence of single movements required to perform an action (Borich *et al.*, 2015). Converging evidence supports that after the intention to move, this movement planning phase is encoded by activity in premotor and supplementary motor regions (e.g., Ionta *et al.*, 2010). Then the signal is translated into a motor command and a replication of the command itself (efference copy) is used to predict the expected motor outcome (forward model) (Von Holst and Mittelstaedt, 1950). Simultaneously, the efference copy is combined with the information about the current body state and entered in a feedforward prediction model (Adams *et al.*, 2013; Wolpert *et al.*, 1998). First, the feedforward model anticipates the somatosensory consequences of the motor command (Blakemore *et al.*, 2000), improving monitoring and error detection. Second, the outcome of the comparison between the expected and the actual somatosensory inflow is volleyed back to the structures encoding the translation of motor planning into motor command, closing the sensory-motor loop (Perruchoud *et al.*, 2014).

At the neural level, the premotor (Desmurget *et al.*, 2009) and supplementary motor regions (Ionta *et al.*, 2010) encode the movement preparation phase. Then the signal is transferred to the motor command node (M1) to trigger the movement (Tanji *et al.*, 1996). Not only does M1 send the signal to the corticospinal tract, but it also generates a copy of the signal (the efference copy) to be entered into the forward model in the parietal cortex (Wolpert *et al.*, 1998). At the same time, the forward model enters information about the estimated movement outcome into the feedforward model, primarily involving the cerebellum (Blakemore *et al.*, 2000). The real somatosensory inflow is first encoded and then compared with the anticipated somatosensory prediction by the activity of basal ganglia, thalamus, and cerebellum (Schlerf *et al.*, 2012). Then the result of this comparison is sent to S1, and premotor and supplementary motor regions (Busan *et al.*, 2009). Based on the acquired information on the current and the estimated body state, S1 (Borich *et al.*, 2015), premotor (Sun *et al.*, 2015) and supplementary motor (Carlsen *et al.*, 2015) regions then project back to M1, in order to calibrate the resulting movement and close the sensory-motor loop (Perruchoud *et al.*, 2014).

Clinically, it can be hypothesized that when afferent somatosensory information is not available (as after complete spinal cord injury), the somatosensory encoding nodes of the sensory-motor loop cannot receive information on the current state and therefore have to rely uniquely on the forward prediction model, causing a general and unsolvable instability of the whole system. This unreliability can trigger a change in the relative weight of kinesthetic and visuospatial body representations. In other words, in pathological conditions affecting the acquirement of the information required to correctly represent the body, we are able to switch strategy in order to use a different reference frame (e.g., visuospatial) and accommodate ecologically appropriate adaptations, e.g., visually guided movements (Rothwell *et al.*, 1982). This interpretation is in line with the evidence suggesting that movement representations are largely multimodal (Halje *et al.*, 2015) and that the interplay between these different representations can change in the case of missing (Curtze *et al.*, 2010), disconnected (Fiori *et al.*, 2014) or misrepresented limbs (Daprati *et al.*, 2010).

5. How to Deliver the Stimulus? Neuro-Robotic Tools to Investigate the Somatosensory System and to Evaluate Artificial Tactile Sensors for Neuroprostheses

The loop between neuroscientific research and biomedical engineering is of major importance for rehabilitation (Pisotta *et al.*, 2015). Neurophysiological studies on the somatosensory system require the precise, repeatable, and unobtrusive delivery of tactile stimuli in controlled situations. This is typically achieved by means of passive touch experimental methods (see Section 2 for illustration of active *versus* passive touch frameworks). In passive touch experiments, the planning and execution of the task underlying the stimulation is external to the subject and hence no voluntary action is required and no efference copy is generated, which has consequences on the brain areas and processes involved (see Section 4 for discussion). The exploration of these sensorimotor relationships is enabled by the development of tools such as mechatronic tactile stimulators suitable for electrophysiological recordings and behavioral studies with psychophysical methods. Several of such platforms have been presented in the literature, with different constructive choices depending on the investigated somatosensory modality (e.g., mechanical, thermal), on the possible combination with the activation of other senses (e.g., vision, audition), on the targeted experimental protocol (e.g., adaptive staircase methods) and experimental environment (e.g., suitable for being applied in combination with microneurography, EEG or MRI studies). In this vein, touch may be a channel for multisensory substitution. This is the case of stimulators with pinned elements, that allow applying both local forces and generalized textures *via* traveling spatiotemporal mechanical waves, and that are used as touch-based assistive devices for visually impaired as well as in neuroscientific investigations (Bliss *et al.*, 1970; Gardner and Palmer, 1989; Hayward *et al.*, 2014; Killebrew *et al.*, 2007; Kyung *et al.*, 2006; Summers and Chanter, 2002; Vidal-Verdú and Hafez, 2007). Tactile stimulation is also used in combination with audio (Ghali *et al.*, 2012) or visual (Lunghi and Morrone, 2013) stimulation to study multisensory integration or to promote an immersive virtual reality experience that was investigated in some cases under magnetic resonance imaging (Duenas *et al.*, 2011; Ku *et al.*, 2003).

Even within one sensory modality, it is crucial to consider all the different aspects that are processed and combined by similar neural mechanisms. For instance, considering somatosensations, some tactile stimulators can deliver to the skin either simple pressure and displacement (Birznieks *et al.*, 2001; Byrne, 1975; Looft and Williams, 1979; Nakazawa *et al.*, 2000; Pawluk and Howe, 1999; Romo *et al.*, 1993; Wheat *et al.*, 2004) or complex texture surfaces (Darian-Smith and Oke, 1980; Goodwin *et al.*, 1985; Johnson and Lamb, 1981; Johnson and Phillips, 1988; LaMotte *et al.*, 1983; Oddo *et al.*, 2011a; Tomassini *et al.*, 2011; Weber *et al.*, 2013; Wiertlewski *et al.*, 2011). However somatosensation is not limited to these features. Indeed, some novel systems also integrate temperature regulation (Bruce, 1982) and, in combination with mechanical stimulation, can be used to investigate multimodal sensory integration, e.g., between temperature and force (Ackerley *et al.*, 2014c; Davis *et al.*, 1998; Klöcker *et al.*, 2014). Such multimodal studies address the investigation of how both mechanical and thermal features of tactile stimuli contribute to the perception of their pleasantness level, hence linking the discriminative and affective components of touch experience. In some devices particular engineering solutions (e.g., shielding techniques, pneumatic actuation and cable driven transmission among several approaches) were introduced in order to allow the delivery of thermal (Davis *et al.*, 1998) or mechanical (Dykes *et al.*, 2007; Golaszewski *et al.*, 2006) stimuli to be compatible with MRI studies, whereas the tactile stimulus delivery was not under automatic control and manual application of calibrated filaments was used (Schaechter *et al.*, 2006) in MRI studies not requiring the dynamic change of stimulation parameters (see Section 3 for discussion with a particular focus on stroke).

In conclusion, the tight integration between robotics and neuroscience enables progression both in the understanding of the somatosensory system (Johansson and Flanagan, 2009; Jörntell *et al.*, 2014) and towards translational neuroprosthetic applications (Saal and Bensmaia, 2015). As a matter of fact, robotics allows closing the loop between sensory and motor domains, especially in cases where physical elements of the body are missing or disconnected, e.g., amputation or spinal cord injury (Pisotta *et al.*, 2015). Also, thanks to these synergies between disciplines, the same experimental platforms and methods applied in neuroscientific research can also be used for the characterization of artificial tactile sensors (Edwards *et al.*, 2008; Fishel and Loeb, 2012; Fishel *et al.*, 2008; Kim *et al.*, 2013; Oddo *et al.*, 2011b; Rongala *et al.*, 2015; Scheibert *et al.*, 2009). According to such synergistic approaches, the same physical stimuli used in human touch studies can be applied for the evaluation of robotic tactile sensors, with similar stimulation conditions such as contact force (typical ranges between tens of mN up to several N) and motion dynamics at stimulus–sensor interface (from few mm/s up to hundreds of mm/s of tangential velocity). In robotic experiments inspired by neuroscientific protocols, the human perceptual thresholds estimated *via* psychophysical methods are used as a benchmarking reference for the results achieved *via* machine learning on sensor data. This approach allows establishing fertile understanding–generation loops prior to porting the artificial touch technology to the afferent pathways of amputees by means of bionic limb prostheses (Dhillon and Horch, 2005; Oddo *et al.*, 2016; Ortiz-Catalan *et al.*, 2014; Raspopovic *et al.*, 2014; Tan *et al.*, 2014).

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